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The women at lowest risk ate a diet high in cereal fiber and polyunsaturated fats, and low in saturated and trans fat. They abstained from smoking and drank moderately.

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10. Passive smoking not so passive for arteries. Secondhand smoke damages the inner layer of the blood vessels, the endothelium, providing the first direct evidence of passive smoking's link to heart disease. Researchers studied 30 Japanese men, average age 27, who were exposed to 30 minutes of passive smoke. A pulsed Doppler echocardiography, a test that measures coronary artery blood flow velocity noninvasively, provided an indication of coronary circulation, including endothelial function.

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American Heart Association

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AHA News
12/31/2001

American Heart Association's top 10 research advances for 2001

2001 Year-end Report

DALLAS, Dec. 31 - New treatments for heart failure - implantable heart devices and cell-grown tissues - are among the top 10 research advances in heart disease and stroke for 2001, says David Faxon, M.D., president of the American Heart Association.
Other major milestones include drug-eluting stents and the use of stem cell transplants to repair stroke-damaged brains.
Created in 1996, the "Top 10" list highlights major gains in heart disease and stroke research.

1. Drug-eluting stents to prevent reblockage of coronary arteries. In what could become one of the biggest breakthroughs in treating cardiovascular disease, scientists used drug-coated stents to prevent the reblockage of the stented section of a coronary artery. Reblockage occurs in about 15 percent to 30 percent of angioplasty patients who receive stents. Researchers involved in several clinical trials have found that stents coated with a drug prevent the overgrowth of cells that typically causes the stented artery to reblock.

The RAVEL study of 238 patients at 19 centers across Europe and Latin America compared patients who received a standard stent to those who received one coated with Sirolimus, an antibiotic that inhibits the overgrowth of cells. The results were presented at September's European Society of Cardiology meeting in Stockholm. No patients who received the drug-eluting stent had restenosis (reblockage) at the seven-month follow-up, but 26 percent of those who received conventional stents had reblockage. Patients who received the drug-eluting stent also had a significant reduction in major cardiac events such as heart attack or death during the follow-up period (3.3 percent vs. 27.1 percent).

Results from ELUTES (European Evaluation of Paclitaxel Eluting Stent) were presented at the American Heart Association's 2001 Scientific Sessions in Anaheim, Calif., in November. The 192 patients in ELUTES were divided into five groups. Four groups received a stent coated with varying doses of the cancer drug. Patients in the fifth group were used as controls. At six-months follow-up, the group that received the stent with the highest dose had a 3.1 percent restenosis rate compared with a 20.6 percent reblockage rate in the control group. A number of other drug-eluting stent trials are under way.

2. Implantable left ventricular assist devices serve as "replacement therapy" for end-stage heart failure. Heart failure patients treated with a left ventricular assist device (LVAD) lived longer and better than patients who did not receive the device. In a study called REMATCH, 68 patients

received the LVAD and 61 patients were treated with drugs and medical monitoring.

Surgeons implanted the pump, which is the size of a compact disc player, into the upper part of the abdominal wall or in the peritoneal lining. A tube on the device enters the left ventricle and drains blood from the ventricle into the device. The pump sends the blood to the aorta. Another tube attached to the pump extends outside the body and is attached to a videotape-sized battery pack, which is worn on a shoulder holster. Patients wear a beeper-sized control system on a belt.

The device assists the heart's left ventricle, which becomes weakened in heart failure. The LVAD lets blood pass from the left ventricle to the aorta, which supplies oxygen-rich blood to the brain and the rest of the body.

In early human trials, researchers tested the LVAD as a "bridge-to-transplant device." This paved the way for its ultimate use - a long-term heart replacement therapy for patients not eligible for heart transplants. An estimated 50,000 to 100,000 people with end-stage heart failure could benefit from this type of therapy.

3. Implantable heart showing promise. On July 2, 2001, 59-year-old Robert Tools became the first person to receive the AbioCor implantable heart. He lived for 151 days. Cause of death was severe abdominal bleeding according to his physician Robert D. Dowling, M.D., of Jewish Hospital in Louisville, Ky., who performed the procedure. Jewish Hospital is one of five sites participating in the AbioCor artificial heart clinical trial.

Tools, like other patients in the trial, had severe heart failure and was too ill for a heart transplant. The trial determined whether the implantable heart can extend life with acceptable quality for patients with less than 30 days' life expectancy, and for whom no other therapeutic alternative exists. To be accepted, patients must have severe heart failure affecting both the left and right ventricles of the heart and have a life expectancy of no more than 30 days.

The heart is implanted in the chest and mimics the function of the human heart by circulating blood through the body. It is battery-operated and weighs only about 2 pounds.

The heart may eventually be an alternative for patients who are candidates for heart transplants but for whom no donor human heart is available. An estimated 4.7 million Americans have congestive heart failure. Many of them would be candidates for a heart transplant, but only about 2,000 donor hearts are available each year in the United States.

4. Tissue engineering with bone marrow and cord blood grows heart parts. Cardiovascular surgery requires replacement parts such as heart valves, blood vessels and vascular patches, but their function may be complicated by blood clots, tissue overgrowth, limited durability, infection and the inability to grow. The body can reject donor tissue. Tissue engineering using a patient's own blood or cells offers an alternative source. It holds particular promise in pediatric surgery where a graft with growth potential is important.

Researchers at the University Hospital Zurich in Switzerland used human

bone marrow cells as a new cell type to engineer heart valves in the laboratory. The cells were seeded on heart valve scaffolds made from bioabsorbable materials and grown in a pulse duplicator bioreactor system that mimics the blood circulation of humans.

Heart valves open and close to let blood flow in only one direction as it is pumped through the heart's chambers. Each valve has several flap-like structures, called leaflets or cusps.

The engineered human valves opened and closed synchronously in the pulse duplicator system. Microscopic examination showed an even cell growth and mechanical function was comparable to natural human heart valves.

In 1999, this group was the first to grow a complete heart valve in the laboratory in a study that used cells from sheep blood vessel walls. The valves showed excellent functional performance in blood circulation and strongly resembled natural heart valves.

Another group used early-stage endothelial cells, called endothelial progenitor cells (EPCs), from human umbilical cord blood to create endothelial layers for cardiovascular tissue engineering. EPCs came from cord blood obtained after a C-section and were culture-grown.

The new cells were seeded onto a bioabsorbable polymer scaffold to make tissue strips with the potential to be molded into any form (valve, vessel, patch, etc.). The cells were treated with vascular endothelial growth factor (VEGF) and fibroblast growth factor (bFGF) to stimulate cell growth. The treated cells were grown in a pulse duplicator system for two weeks. The cells formed capillary-like tubes, indicating the start of blood vessel formation.

The researchers concluded that human umbilical cord blood is a valuable source of EPCs, providing novel cells for tissue engineering.

The exciting possibilities for this cell source include "banking" the cells for future use. Cord blood cells could potentially be used to create a tissue-engineered structure needed to correct a cardiac birth defect diagnosed prenatally. The new tissue could be ready to use when the baby is born - or even before birth for potential prenatal/fetal surgical repair.

In other cell transplant experiments, adult human cardiac myocytes (heart muscle cells) regenerated after heart attack. This means the heart may be able to replace damaged tissue by producing new functional cells. A subpopulation of myocytes that is not "terminally differentiated" re-entered the cell cycle and divided after the infarction. In similar research, adult stem cells derived from bone marrow regenerated, forming new functional heart cells when injected around the site of the heart attack.

5. Gene therapy shown to reduce angina. Experimental treatments using genes for vascular endothelial growth factor (VEGF) are not new. But in 2001 researchers brought a new twist to this pioneering treatment for coronary artery disease.

For the first time, researchers have data from a randomized, blinded, placebo-controlled trial indicating that blood flow to the heart improves

after VEGF2 treatment. Patients treated with the VEGF2 gene had less angina, increased their ability to exercise and had improved myocardial perfusion. Placebo treated patients had none of these changes.

VEGF is a naturally occurring protein that stimulates the proliferation and migration of endothelial cells and endothelial progenitor cells, leading to formation of new blood vessels. The theory is that injecting the gene into the heart triggers the growth of new blood vessels in the oxygen-starved heart muscle.

Previous trials suggested that gene transfer of VEGF diminished chest pain and increased blood flow to the heart. However, those studies used a surgical approach to directly inject the gene into the heart. Thus, it wasn't possible to have a placebo-controlled trial, a major limitation of the trials.

In the study, 19 patients with class III or IV angina - the most severe chest pain associated with heart disease - received six injections in their left ventricle of either a placebo solution (saline) or a VEGF2 gene therapy solution. The injections were made using a special catheter that can identify areas of the heart muscle that lack an adequate blood supply. The patients all tolerated the gene delivery procedure without complications.

Angina improved by two to three classes in eight of 12 patients who received the VEGF2 gene. One person reported that VEGF2 gene therapy completely eliminated chest pain. None of the six placebo patients experienced a significant reduction in angina class. The difference in outcome between the VEGF2- and placebo-treated patients was statistically significant, a surprising fact in this relatively small pilot study. A large, randomized trial is being planned.

6. Cholesterol-lowering drugs bring benefits to high-risk populations, even when LDL is normal. The MRC/BHF Heart Protection Study (HPS) is the world's largest randomized trial of cholesterol-lowering drugs and of antioxidant vitamins in people at increased risk of coronary heart disease (CHD). Even though they have been used for decades, statin drugs' usefulness in particular populations is unknown. The study is one of the first to include substantial numbers of people in categories that were excluded from other studies of this kind.

Patients aged 40-80 with a history of occlusive vascular disease or diabetes were eligible, provided their doctors did not consider statin therapy a clear choice. Between July 1994 and May 1997, 20,536 patients were recruited in 69 United Kingdom hospitals. Previous heart attack was reported by 8,510 (most of whom were elderly, female or had "low" total cholesterol levels). They also had other forms of cardiovascular disease such as previous stroke or TIA, peripheral artery disease, diabetes (with overlap between these categories).

Participants were randomly allocated 40 mg of simvastatin daily or matching placebo for 5 ½ years. Vitamins were given to half of each treatment group (600 mg vitamin E, 250 mg vitamin C, 20 mg beta-carotene daily). The other half received a placebo. The vitamins had no effect on vascular or related death or disease.

Cholesterol-lowering therapy reduced total and vascular mortality, total CHD, stroke, and revascularization procedures. After making allowance for non-compliance (including non-study statin use), simvastatin given at 40

mg daily reduced "major vascular events" by at least one-third among patients (women, people over 70 years old, those with LDL below 3.0 mmol/l [116 mg/dL] and those with diabetes or non-coronary occlusive disease without pre-existing CHD).

Further development in treating lipid disorders came from recommendations from the National Cholesterol Education Panel (NCEP). They suggest a new approach to treat adults with elevated blood cholesterol. The recommendations, the NCEP Adult Treatment Panel III (ATP III), call for physicians to use "the basic principle" to match the intensity of the therapy to the person's risk. A table that estimates a person's 10-year risk is used as a guide for treatment goals. Risk is calculated by adding points based on the presence of risk factors such as elevated cholesterol, smoking status, blood pressure, HDL and age. Individuals with two or more risk factors should be treated more intensely.

Other new features of ATP III focus on treating diabetes, multiple metabolic syndrome and other risks factors. The panel supports a complete lipoprotein profile: total, LDL and HDL cholesterol and triglyercerides, rather than screening for total cholesterol or HDL alone. It presents strategies for promoting lifestyle changes to reduce risk and drug therapies. The report recommends new targets for optimal LDL levels. Optimal levels of LDL are 100 mg/dL or less; and low HDL optimal levels should be from 35 to 40 mg/dL. The triglycerides classification cut point has been lowered.

Primary prevention of cardiovascular disease should begin with reducing intakes of saturated fat, increased physical activity and weight control. Secondary prevention should include reducing LDL cholesterol below 100 mg/dL by lifestyle changes and drug therapy.

7. New genetic predictors of cardiovascular disease. In one of the largest genetic studies of its kind, researchers discovered three genetic variants that may explain why some families are prone to premature heart disease. Investigators at 15 institutions used "high throughput" microarray genotyping to sift through 62 genes of 352 people with coronary artery disease and 418 individuals without. The culprit genes regulate thrombospondins (TSP), a family of matrix proteins that helps blood clot and repair arteries.

The investigators discovered distinctive variations in the genes of families with coronary artery disease, including a protective one. Changes known as single-nucleotide polymorphisms (SNP) were observed in genes that encode the different thrombospondin proteins. These proteins govern new blood vessel growth, blood clotting and the blood vessel response to oxidized low-density lipoprotein cholesterol (LDL).

In the families with coronary artery disease, at least two members had a heart attack or coronary revascularization at a young age - before age 45 in men and age 50 in women. The variant identified as thrombospondin-1 (TSP-1) was associated with a nine-fold risk of premature heart attack. Those with the TSP-4 variant had an 89 percent greater risk of heart attack. The TSP-2 variant was linked to a 69 percent lower heart attack risk.

Individuals with two copies of one of the variants, called the missense

variant in thrombospondin-1, had a higher risk of early heart disease and the lowest levels of thrombospondin-1 in blood tests. Individuals with variants of the TSP gene tended to have low levels of thrombospondin. The study, the largest genotyping of cardiovascular risk to date, may help unravel the major causes of death and disability.

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10. Passive smoking not so passive for arteries. Secondhand smoke damages the inner layer of the blood vessels, the endothelium, providing the first direct evidence of passive smoking's link to heart disease. Researchers studied 30 Japanese men, average age 27, who were exposed to 30 minutes of passive smoke. A pulsed Doppler echocardiography, a test that measures coronary artery blood flow velocity noninvasively, provided an indication of coronary circulation, including endothelial function.

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American Heart Association

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Device for Clogged Arteries Gets a Boost

By LAWRENCE K. ALTMAN
Published: Tuesday, January 16, 2001

Over the last 15 years, the use of stents -- wire mesh tubes placed in coronary arteries to prop them open after unblocking -- has soared. But a persistent problem has been that in many cases, stent insertion causes scarring and renewed blockage.

Now doctors in Brazil and the Netherlands who pioneered earlier versions of stents have found that coating the metal device with an immune suppressing drug can safely prevent formation of scar tissue.

The drug, known as rapamycin or Rapamune, is marketed by Wyeth-Ayerst Laboratories, a division of American Home Products, to prevent kidney transplant rejection by preventing cell growth. Such growth forms scars. The stent is made by the Cordis Corporation of Warren, N.J., a subsidiary of Johnson & Johnson, which paid for the pilot studies and is calling the drug sirolimus.

Early findings from the first human tests of the experimental coated stent conducted by Dr. J. Eduardo Sousa's team in Sao Paulo, Brazil, are being reported today in Circulation, a scientific journal published by the American Heart Association.

The journal's editor, Dr. James T. Willerson, who also heads the department of medicine at the University of Texas-Houston Medical School, designated Dr. Sousa's article "as breakthrough information." After arteries are cleared of blockage, they can become clogged again by blood clots, scarring or new deposits of fatty substances. This study showed that the sirolimus-coated stent prevented the scarring, known as intimal proliferation, and often the need for repeat procedures, known as angioplasties, to unblock arteries for eight months after implantation.

Although the pilot studies were designed chiefly to test safety, they ended up showing significant benefit. In the Netherlands, Dr. Patrick W. Serruys said his team at Erasmus University in Rotterdam had confirmed Dr. Sousa's findings in an unpublished study of 15 other patients. They were tested six months after they received the same coated stent used in Brazil.

Much work needs to be done to determine the sirolimus stent's place in everyday medical practice, leading cardiologists said. But they also said that if larger studies supported the early findings, the coated stent could eventually reduce the need for coronary bypass surgery for many people and mark a new era in treating heart disease, the leading killer of Americans.

"The early data is so compelling that most of us who have reviewed it are extraordinarily excited," said Dr. Paul S. Teirstein, a stent expert at the Scripps Clinic in San Diego.

Dr. Serruys said that although other experts expressed surprise at his enthusiasm for the

Health Update

stent, he viewed its development "as a turning point in cardiology."

"And I will be very surprised if I made a major mistake in judgment there," he said.

Another stent expert, Dr. Spencer B. King III of Piedmont Hospital and Emory University in Atlanta, said he was encouraged by the early findings but wished cardiologists would "turn down the rhetoric a little." The pilot trials "cry out for" larger and more rigorously designed studies known as randomized, double-blind, placebo-controlled trials to provide definitive answers, Dr. King said.

In such trials, participants agree to receive either a sirolimus-coated stent or a standard stent. The choice is made by the equivalent of a flip of a coin, and neither the doctor nor the recipient knows whether the implanted stent is coated or not. The trials are also designed to detect unexpected long-term complications from the drug.

Stents are implanted as part of angioplasty, a standard technique in which a balloon-tipped tube is inserted in an artery in the upper leg and threaded to the affected artery, where it is inflated to remove the blockage. After repair, a stent can be left in place to provide a permanent scaffolding.

Vice President-elect Dick Cheney received a standard stent in November after his fourth heart attack.

The pressure that clears a clogged artery also leads the blood vessel to react as if it were injured. The artery forms scar tissue in and at the edges of standard stents that, depending on circumstances, can cause significant new clogging in up to 25 percent of cases, a process known restenosis.

Since a stent was first implanted in a coronary artery in Europe in 1986, cardiologists have sought to improve them. The ideal healing would be limited growth -- a thin layer of cells to carpet the stent-injured area on the inside wall of the artery, rather than thicker scarring. Early attempts to coat stents with a drug to prevent scarring failed; some made the scarring worse.

More recently, stents that have been coated with a drug, heparin, have been licensed for reducing the frequency of clot formation at or near the site of implantation. Other licensed stents use radiation and are implanted within stents that became blocked and need to be unclogged in a second go-round. Researchers are also testing stents coated with taxol, an anticancer drug, and other drugs to prevent excessive cell growth or scarring.

Dr. Sousa said he had been impressed with findings from experiments in which rapamycin on its own was injected into pigs with blocked arteries at the Mount Sinai Hospital in Manhattan. Then, after Cordis developed a way to limit the effect of rapamycin to the area of the stent, Dr. Sousa said the company asked his team at the Dante Pazzanese Institute of Cardiology in Sao Paulo to begin implanting them experimentally. In December 1999, 15 patients received a slow-acting form that was released over a period of about four weeks. Last February, another group of 15 received a fast-acting form released over two weeks.

The sirolimus stents remained open eight months after implantation in all 30 patients, and none experienced a heart attack, needed a repeat procedure or died.

Dr. Sousa said he was "completely surprised" when findings from angiography and intravascular ultrasound tests showed both the fast and slow forms limited the cell growth in the unblocked arteries and did not cause renarrowing. Two teams independently confirmed the findings, he said.

On Dec. 12, one year after the coated stents were implanted, Dr. Sousa said he retested the first 15 patients and still found no sign of the scarring. He also said he was impressed by the lack of scar formation among diabetics, who tend to have higher rates of reblockage

than nondiabetics.

The findings may dispel doubts expressed by skeptical cardiologists at earlier scientific meetings who asserted that the coated stent's benefit would not be long-lasting, Dr. Sousa said in a telephone interview.

Cordis is paying for two studies using the slow-acting form of sirolimus stents.

In the first, stents were implanted in 220 patients in European, Mexican and South American hospitals last year. Retesting is due to be completed by June, and early findings are expected later this year.

The second study will involve more than 1,000 patients in 55 medical centers in the United States. Its start awaits approval from the Food and Drug Administration, a Cordis spokesman said. Participants will be tested periodically for up to three years with angiograms and intravascular ultrasound, a three-dimensional imaging method to precisely define how much scar forms.

"That will be a definitive trial that shows that either this stent is the greatest thing to hit the angioplasty world or, in fact, it's another one of many early trials that didn't pan out," Dr. Teirstein said.

Photo: A metal stent, with a detail of its mesh, is being coated with an immune suppressing drug in experiments aimed at preventing scar tissue from forming in coronary patients. (Cordis Corp.)

A version of this article appeared in print on Tuesday, January 16, 2001, on section F page 8 of the New York edition.

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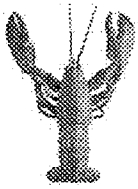
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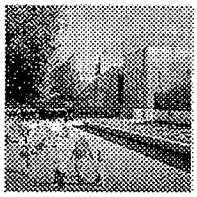
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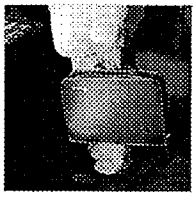
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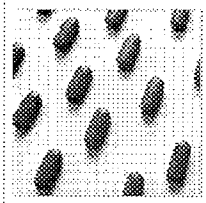
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Randomised trial of excimer laser angioplasty versus balloon angioplasty for treatment of obstructive coronary artery disease

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Summary

Background Excimer laser coronary angioplasty is reported to give excellent procedural results for treatment of complex coronary lesions, but this method has not been compared with balloon angioplasty in a randomised trial.

Methods Patients (n=308) with stable angina and coronary lesions longer than 10 mm on visual assessment were included. 151 patients (158 lesions) were assigned randomly to laser angioplasty and 157 (167 lesions) to balloon angioplasty. The primary clinical endpoints were death, myocardial infarction, coronary bypass surgery, or repeat coronary angioplasty of the randomised segment during 6 months of follow-up. The primary angiographic endpoint was the minimal lumen diameter at follow-up in relation to the baseline value (net gain), as determined by quantitative coronary angiography.

Findings Laser angioplasty was followed by balloon angioplasty in 98% of procedures. The angiographic success rate was 80% in patients treated with laser angioplasty compared with 79% in patients treated with balloon angioplasty. There were no deaths. Myocardial infarction, coronary bypass surgery, and repeat angioplasty occurred in 4·6%, 10·6%, and 21·2%, respectively, of the patients in the laser angioplasty group compared with 5·7%, 10·8%, and 18·5% of the balloon angioplasty group. Net mean (SD) gain in minimal lumen diameter was 0·40 (0·69) mm in patients treated with laser angioplasty and 0·48 (0·66) mm in those treated with balloon angioplasty (p=0·34). The restenosis rate (>50% diameter stenosis) was 51·6% in the laser angioplasty group versus 41·3% in the balloon angioplasty group (p=0·13).

Interpretation Excimer laser angioplasty followed by balloon angioplasty provides no benefit additional to balloon angioplasty alone with respect to the initial and long-term clinical and angiographic outcome in the treatment of obstructive coronary artery disease.

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Introduction

Excimer laser coronary angioplasty (ELCA) is one technique used for treatment of obstructive coronary artery disease. The excimer laser system exhibits favourable characteristics for ablation of atherosclerotic tissue compared with other laser devices because of its small penetration depth and the induction of limited damage to the vascular wall.[1–3] Compared with results after balloon angioplasty,[4] prospective non-randomised studies of ELCA[5–9] showed a substantial improvement in primary success rate and procedural complications in patients with complex coronary lesions. These promising results warranted a randomised trial to establish the role of laser angioplasty as an alternative approach in the treatment of obstructive coronary artery disease. Most patients considered suitable for coronary angioplasty have long (>10 mm) coronary lesions. These considerations led us to undertake a randomised trial to evaluate initial and long-term clinical and angiographic outcome of ELCA compared with balloon angioplasty in patients with long coronary lesions.

Methods

Selection of patients

After completion of a pilot phase including 71 patients,[6] the multicentre Amsterdam-Rotterdam (AMRO) trial was started in September, 1991, and completed in November, 1993. Based upon the results of nonrandomised studies of ELCA, we expected the primary procedural success rate after ELCA to be greater than 85% and less than 70% after balloon angioplasty. Thus, with an alpha-error of 0·05 and a beta error of 0·20, 120 patients with complete follow-up were required in each treatment group. 300 patients were considered necessary for inclusion taking into account that 20% of the patients were not eligible for follow-up angiography. All patients (either with single or multivessel disease) with stable angina pectoris, coronary lesions longer than 10 mm on visual assessment, and total or functional

occlusions (thrombolysis in myocardial infarction [TIMI] flow grade 0 or 1)[13] who were suitable for coronary angioplasty were screened for inclusion in the trial. Clinical exclusion criteria were: unstable angina, myocardial infarction within the previous 2 weeks, a life expectancy of less than 1 year, and factors that made clinical or angiographic follow-up difficult. Angiographic exclusion criteria were: intended angioplasty of a venous bypass graft, unprotected left main disease, extreme tortuosity of the vessel, highly eccentric lesions, vessels with ostial lesions, angulated lesions of more than 45°, bifurcation lesions, aorta-ostial lesions, lesions with angiographic evidence of a thrombus or dissection, and total occlusions with a low likelihood of passage with a guide wire.[13] The protocol was approved by the institutional review boards of the participating centres.

Randomisation

Patients were assigned randomly by telephone from a central office to laser angioplasty or balloon angioplasty after eligibility had been established and written informed consent obtained. Lesions suitable for balloon angioplasty only were indicated before the randomisation in patients with multiple lesions. All coronary lesions in a patient who fulfilled the selection criteria were treated according to the same treatment allocation.

Laser angioplasty and balloon angioplasty

Patients' anti-anginal medication was continued until the procedure. A calcium antagonist (nifedipine 20 mg three times a day) was added during in-hospital stay. Acetyl salicylic acid (250–500 mg daily) was given a day before the procedure and continued for 6 months afterwards. The excimer laser systems (wavelength 308 nm) used were: the Dymer 200+ (Advanced Interventional Systems Inc, Irvine, CA, USA), with a pulse duration of 210 ns and a repetition rate of 20 Hz, delivered by multifibre over wire laser catheters with a diameter of 1·3, 1·6, or 2·0 mm, at a fluence of 45–65 mJ/mm^2; and the CVX-300 system (Spectranetics, Colorado Springs, CO, USA), which emits a pulse duration of 135 ns at a repetition rate of 25 Hz, delivered by 1·4, 1·7 or 2·0 mm laser catheters, with a similar fluence. The 1·3z mm laser catheter was used after its introduction in 1992. The 1·3/1·4 mm laser catheter was used for vessels with diameter of 1·8–2·3 mm, 1·6/1·7 mm laser catheter for vessels with a diameter of 2·3–3·0 mm, and 2·0 mm laser catheter for vessels with a diameter of 3·0 mm or more.

Cardiac catheterisation in all patients was by the percutaneous femoral approach. Heparin was administered intravenously to maintain the activated clotting time at more than 400 s and was continued for at least 12 h after the procedure. After crossing the lesion with the guide wire, the laser catheter was advanced at a speed of about 1 mm/s. A larger laser catheter was used if the angiographic result was unsatisfactory after one passage of the laser catheter. Additional balloon angioplasty was done to optimise the angiographic result. Serum creatine kinase myocardial band concentration was measured routinely within 12 h after the initial procedure.

Quantitative coronary angiography

Quantitative coronary angiography, before and after the procedure and at 6 months' follow-up, was done after administration of 0·1–0·3 mg of nitroglycerin or 1–3 mg of isosorbine dinitrate by the intracoronary route. The angiograms were analysed, in a central laboratory with the computer-assisted cardiovascular angiography analysis system (CAAS) for determination of the interpolated reference diameter, the minimal lumen diameter, and the percentage diameter stenosis.[12] Lesion length was determined by the maximal lesion length between the crossing point of the computerised contour detection line and the interpolated reference diameter line. If a revascularisation procedure involving the treated segment had been done before the angiography at 6 months, the most recent angiogram obtained before this intervention was used as the follow-up angiogram regardless of the timing of the second intervention. If the time from intervention to follow-up angiography was less than 3 months and no second intervention was performed, the patient was asked to undergo angiography again after 6 months. In the absence of a second angiogram at 6 months, the angiogram obtained most recently within the previous 3 months was used.

	ELCA	Balloon angioplasty
Number of patients	151	157
Clinical characteristics		
Mean (range) age (yr)	58·1 (32–83)	59·4 (35–79)
Sex (male/female)	115/36	114/43
Smoking status		
Never	41	50
Previous	74	68
Current	33	36
Unknown	3	3
Diabetes mellitus	15	20
Previous conditions		
History of hypertension	57	50
History of hypercholesterolaemia	58	59
History of stroke	4	5
History of peripheral vascular disease	9	14
Myocardial infarction	70	68
Coronary artery bypass grafting	10	13
Balloon angioplasty	16	25
Exertional angina (CCS class*)		
I	11	8
II	44	49
III	82	85
IV	14	14
Non exertional angina	77	81
Mixed angina	76	80
Medication at screening		
Nitrates	95	108
Ca-antagonists	122	133
Beta-blockers	120	113
Monotherapy	25	20
Double therapy	57	65
Triple therapy	66	68
No therapy	3	4
Extent of coronary artery disease		
One vessel disease	83	79
Two-vessel disease	51	63
Three-vessel disease	17	15
Number of lesions	159	167
Angiographic characteristics		
Location of lesion		
Right coronary artery	56	61
Left anterior descending	62	64
Left circumflex	41	42
Type of lesion†		
A	1	0
B1	0	2
B2	83	71
C	74	94
Ulcerated	53	55
Multiple irregularities	83	97
Calcified	33	39
Eccentric	100	104
Tandem	18	26
Length by visual assessment (mm)		
<10	1	3
10–20	122	109
>20	33	44
Unknown	2	11
Grade of perfusion‡		
0	26	27
I	23	27
II	27	24
III	85	80

*According to classification of Canadian Cardiovascular Society.[11] †According to modified American College of Cardiology/American Heart Association task force criteria.[11] ‡According to TIMI-study group.[13]

Table 1: Base-line clinical and angiographic characteristics of 308 patients included in the intention-to-treat analysis

Clinical and angiographic follow-up

Patients were seen after 1 and 6 months for an interview, physical examination, and electrocardiogram. Follow-up coronary angiography was done after 6 months. Repeat intervention was

performed based on recurrent symptoms of angina and/or objective evidence of myocardial ischaemia and a diameter stenosis of more than 50% on visual assessment.

End-points

Primary clinical end-points were the occurrence of any of the following events during a 6 month (±1 month) follow-up: cardiac death, myocardial infarction (based on the presence of at least two of the following: typical chest pain and/or a serum rise of more than twice the normal upper limit of the creatine kinase myocardial band level and/or new pathological Q-wave formation on the electrocardiogram), coronary bypass surgery, or a second angioplasty because of recurrent symptoms of angina and/or objective evidence of myocardial ischaemia by positive exercise testing related to the randomised segment. Coronary bypass surgery was defined to include emergency (within 12 h after the procedure) or elective bypass surgery. All the clinical events were reviewed by the critical-event committee, which was unaware of the treatment assignment.

Primary angiographic end-point was the minimal lumen diameter at the treated coronary site at 6 months follow-up relative to the baseline value before the procedure (net gain). Secondary end-points were: (1) laser success defined as a more than 20% reduction in diameter stenosis after laser angioplasty only on visual assessment; (2) angiographic success defined as a less than 50% residual stenosis at the end of the procedure on visual assessment; (3) acute gain defined as the minimal lumen diameter at the treated coronary site at the end of the procedure relative to the baseline value; (4) functional class at 6 months according to the classification of the Canadian Cardiovascular Society;[15] (5) the percent diameter stenosis at the treated coronary site at 6 months' follow-up relative to the baseline value (net gain in percentage diameter stenosis); (6) restenosis rate defined as a more than 50% diameter stenosis at the treated coronary site at 6 months' follow-up angiography as determined by automated contour detection analysis; and (7) late loss defined as the minimal lumen diameter at the treated site at 6 months' follow-up relative to the minimal lumen diameter after the procedure.

Statistical analysis

Continuous variables (age, reference diameter, lesion length, percentage diameter stenosis, and minimal lumen diameter) were expressed as mean (SD) and were compared with the unpaired *t* test. Chi-squared analysis and Fisher's exact test for two by two tables were used to compare dichotomous variables. Clinical events and angiographic complications were compared by relative risk (RR) and 95% confidence interval. A p value less than 0·05 was considered statistically significant.

Results

Patient characteristics and randomisation

313 consecutive patients (330 lesions) were randomly assigned to ELCA (155 patients/162 lesions) or balloon angioplasty (158 patients/168 lesions). In five patients (four assigned to laser angioplasty, one to balloon angioplasty) the randomised segment was not treated. Of these five patients, one withdrew his informed consent and received balloon angioplasty. Two patients received no coronary intervention because the randomised segment showed a non-significant stenosis on the pre-procedural angiogram. One patient was randomised twice. The randomised segment was not treated in one patient due to emergency coronary bypass surgery after treatment of a non-randomised segment. These five patients were not included in the final analysis since there was no intention for treatment according to randomisation.

Clinical and angiographic baseline characteristics of the remaining 308 patients were similar and are shown in table 1. Approximately half of the patients had multivessel disease and 50% had experienced a previous myocardial infarction. One third of the randomised coronary segments were total or functional coronary occlusions (TIMI 0 or 1).

158 lesions (151 patients) were randomly assigned to ELCA. ELCA could not be done during 25 procedures (25 patients) because of inability to cross the coronary lesion with any guide wire (16 lesions), or cross-over to balloon angioplasty (in total nine lesions: five because of inability to pass the guide wire, three due to technical failure of the laser system, and one because of presumed risk of perforation). Of the remaining 133 lesions, 130 were treated with additional balloon angioplasty to obtain an optimal angiographic result. Standalone laser angioplasty was done with three lesions (2%). In 89 of the 133 (67%) treated lesions, a laser catheter not larger than 1·3/1·4 mm was used. In 19 lesions more than one laser catheter was used.

167 lesions (157 patients) were randomly assigned to balloon angioplasty. Balloon angioplasty was not done during 22 procedures because the lesion could not be crossed with a guide wire. In two patients the lesion could not be crossed with the balloon; one of these was successfully treated with laser angioplasty only and one with laser angioplasty followed by balloon angioplasty. The remaining 143 lesions were treated with balloon angioplasty only.

Procedural results

The intention-to-treat analysis yielded a laser success by visual assessment in 68% (107 lesions) of the 158 lesions randomly assigned to ELCA. The angiographic success rate by visual assessment was 80% (126 lesions) in patients treated with ELCA compared with 79% (132 lesions) in patients treated with balloon angioplasty. The angiographic success rate by quantitative coronary angiography yielded similar results (80% in patients assigned to ELCA compared with 78% in patients assigned to balloon angioplasty).

The per protocol analysis yielded a success rate of 81% after ELCA, which increased to 91% after additional balloon angioplasty in patients allocated to ELCA compared with an angiographic success rate of 92% in

	ELCA (n=151)	Balloon angioplasty (n=157)	Relative risk (95% CI)	p
Death	0	0	..	..
Myocardial infarction	7 (4·6)	9 (5·7)	0·81 (0·31–2·12)	0·67
Q-wave	4 (2·6)	3 (1·9)	1·39 (0·32–6·10)	0·72
Periprocedural	2 (1·3)	2 (1·3)	1·04 (0·15–7·29)	0·97
Follow-up	2 (1·3)	1 (0·6)	2·08 (0·19–22·70)	0·54
Non-Q-wave	3 (2·0)	6 (3·8)	0·52 (0·13–2·04)	0·50
Periprocedural	3 (2·0)	3 (1·9)	1·04 (0·21–5·07)	0·96
Follow-up	0	3 (1·9)	0·15 (0·01–2·85)	0·09
Coronary artery bypass grafting	16 (10·6)	17 (10·8)	0·98 (0·51–1·87)	0·85
Periprocedural	7 (4·5)	3 (1·9)	2·43 (0·64–9·21)	0·16
Follow-up	9 (6·0)	14 (8·9)	0·67 (0·30–1·50)	0·32
Repeat angioplasty	32 (21·2)	28 (18·5)	1·15 (0·73–1·80)	0·55
Periprocedural	2 (1·3)	3 (1·9)	0·69 (0·12–4·09)	0·68
Follow-up	30 (19·9)	26 (16·6)	1·20 (0·75–1·93)	0·45
Primary clinical endpoint*	50 (33·1)*	47 (29·9)	1·11 (0·80–1·54)	0·55

*Death, myocardial infarction, coronary artery bypass grafting, or repeat angioplasty.

Table 2: **Number (%) clinical events during the procedure and 6 months' follow-up**

	ELCA	Balloon angioplasty	Difference (95% CI)	p
Number of lesions	124	126	..	..
Reference diameter* (mm)	2·51 (0·47)	2·47 (0·53)	..	..
Length (mm)	17·69 (5·58)	18·82 (7·15)	..	..
Diameter stenosis (%)				
Before angioplasty	68·5 (18·3)	68·9 (18·6)	..	..
After angioplasty	37·6 (10·3)	37·9 (8·9)	−0·4 (−2·6 to 2·0)	0·76
At follow-up	56·1 (23·3)	52·6 (23·4)	3·4 (−2·4 to 9·3)	0·25
Restenosis (%)	51·6	41·3	10·3 (−2·0 to 22·6)	0·13
Minimal lumen diameter (mm)				
Before angioplasty	0·77 (0·44)	0·77 (0·47)	..	..
After angioplasty	1·69 (0·41)	1·59 (0·34)	0·10 (0·01 to 0·19)	0·05
At follow-up	1·17 (0·71)	1·25 (0·68)	−0·08 (−0·25 to 0·09)	0·34
Net gain† (mm)	0·40 (0·69)	0·48 (0·66)	−0·08 (−0·25 to 0·09)	0·34
Acute gain‡	0·92 (0·53)	0·82 (0·50)	0·10 (−0·03 to 0·23)	0·15
Late loss§ (mm)	0·52 (0·70)	0·34 (0·62)	0·18 (0·15 to 0·35)	0·04

Figures are mean (SD) unless indicated.
*Reference values are interpolated diameters of normal vessels; †minimal lumen diameter (MLD) at follow-up minus MLD before initial procedure; ‡MLD after initial procedure minus MLD before initial procedure; §MLD after initial procedure minus MLD at follow-up.

Table 3: **Quantitative analysis**

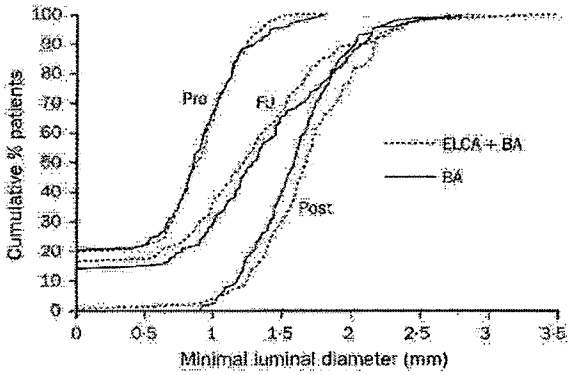

Figure: **Cumulative frequency distribution curves**
Minimal luminal diameters are shown before the initial intervention (Pre), after the initial intervention (Post), and at follow-up angiography (FU) for 151 patients treated with ELCA followed by additional balloon angioplasty (ELCA+BA) and 157 patients treated with balloon angioplasty (BA).

patients allocated to balloon angioplasty (RR 0·99, 95% CI 0·92–1·06; p=0·69).

There were no deaths. The incidence of Q-wave and non-Q-wave myocardial infarctions was similar in both groups (table 2). Most non-Q-wave myocardial infarctions were small in both groups (maximal creatine kinase-myocardial band concentration <20 U/L).

Seven patients (4·5%) randomly assigned to ELCA required emergency coronary bypass surgery for the following reasons: severe dissection of the randomised segment (four patients, two of whom were treated with stenting as a bridge to coronary bypass surgery), perforation of the randomised segment (one patient), extravasation of contrast (one patient), and unstable angina (one patient). Emergency coronary bypass surgery was required in three patients (1·9%) randomly assigned to balloon angioplasty due to the occurrence of a severe dissection.

Intimal dissections after completion of the procedure occurred in 74 lesions (46·8%) in the patients treated with ELCA. Most of these dissections (91%) were minor: type A in 27 lesions, type B in 22 lesions, and type C in 18 lesions.[16] The dissection rate was similar in patients treated with balloon angioplasty (54·5% [91 lesions] of patients) with 90% of dissections being minor: type A in 33 lesions, type B in 37 lesions, and type C in 12 lesions. The procedure was complicated by coronary spasm in seven patients treated with ELCA and in two patients treated with balloon angioplasty (RR 3·70, 95% CI 0·78–17·54; p=0·1). Coronary perforation resulting in haemodynamic deterioration occurred in one patient in the ELCA group. This complication did not occur in the balloon angioplasty group. The incidence of transient occlusions of the randomised segment was significantly higher in patients allocated to ELCA (ten patients) than in those allocated to balloon angioplasty (one patient) (10·57, 1·37–81·62; p=0·005).

Clinical and angiographic outcomes

Clinical follow-up was complete in 98% of patients. A primary clinical end-point was reached in 50 patients (33·1%) treated with ELCA versus 47 patients (29·9%) treated with balloon angioplasty. The incidences of myocardial infarction, coronary bypass surgery, and repeat angioplasty were similar in both groups (table 2).

Of the 151 patients randomly assigned to ELCA, 91 patients had no angina, 17 patients were graded as functional class I, 31 patients as class II, 11 patients as class III, and one patient as class IV according to the Canadian Cardiovascular Society classification criteria[15] after 6 months' follow-up. Of the 157 patients randomly assigned to balloon angioplasty, 94 patients had no angina, 17 patients were graded as functional class I, 27 patients as class II, 17 patients as class III, and two patients as class IV after 6 months' follow-up.

Follow-up angiography was not requested in 22 of the 151 patients in the ELCA group due to failure of the initial procedure or coronary bypass surgery. Repeat angiography was performed in 120 of the remaining 129 patients (93%). Follow-up angiography in the balloon angioplasty group was requested in 131 of the 157 patients. Repeat angiography was done in 123 of these patients (91%).

The net gain in minimal lumen diameter was similar in both groups (table 3). The net gain in the ELCA group was the result of a small, but non-significant, increase in the acute gain minus a significant greater late loss compared with the balloon angioplasty group. The cumulative distribution of the minimal lumen diameter is shown in the figure. The net mean (SD) gain in diameter stenosis was 12·4 (25·1)% in the ELCA group versus 16·2 (25·9)% in the balloon angioplasty group (difference −3·9%, 95% CI −10·2 to 2·5; p=0·2). The incidence of restenosis was 51·6% in the ELCA group compared with 41·3% in the balloon angioplasty group (p=0·13).

Discussion

The purpose of this randomised study was to compare the clinical and angiographic outcome of ELCA versus balloon angioplasty in the treatment of longer (>10 mm) coronary lesions. The more recent data from ELCA registries indicate an increased use of additional balloon angioplasty, which is consistent with the results of our study.[16–18] ELCA was followed by balloon angioplasty in 98% of procedures and therefore this trial in fact comprises a comparison between combined ELCA and balloon angioplasty versus balloon angioplasty only.

We have shown that ELCA and balloon angioplasty for the treatment of obstructive coronary artery disease yield similar initial and long-term clinical and angiographic outcomes in a selected cohort of patients with stable angina and coronary lesions longer than 10 mm.

Clinical outcome for primary clinical and angiographic end-points were similar in both groups. With respect to the differences observed, there was a significantly higher rate of transient occlusions in the ELCA group compared with the balloon angioplasty group (6·3% vs 0·6%). This may be explained by a response of the vascular wall due to the mechanical effects caused by a fast expanding and imploding vapour bubbles generated during ELCA.[19,20] In general, this complication can be dealt with by administration of intracoronary nitroglycerin and additional balloon angioplasty.

Furthermore, there was a significant greater late loss in minimal lumen diameter in the ELCA group compared with the balloon angioplasty group. This finding may be related to an accelerated degree of neointimal response due to the mechanical effects of rapid vapour bubble formation during laser application or a negative influence on the geometric remodelling process after intracoronary interventions.[21,22] The greater late loss in minimal lumen diameter resulted in a higher restenosis rate after ELCA—51·6% versus 41·3% in the balloon angioplasty group.

It is difficult to compare the results of the present study with data from non-randomised ELCA registries.[6,8,9,16–18] Most of these registries focus attention on the initial results after laser angioplasty and have reported completeness of angiographic follow-up in 73–88% of patients after successful ELCA. In our trial, the clinical follow-up was complete in 98% of patients in both groups, and angiographic follow-up was complete in 93% of patients in the ELCA group and 91% of patients in the balloon angioplasty group. Furthermore, patients included in the registries had a variety of coronary lesions and the reported procedural success rates relate to those procedures in which the coronary lesion was successfully crossed with the guide wire. This explains why success rates in our study based on the intention-to-treat analysis are lower than in the ELCA registries, whereas results of the per protocol analysis are comparable to the registry data. Moreover, quantitative coronary analysis was performed by an independent core laboratory, whereas most angiographic results in the registries were based on visual assessment or semi-quantitative assessment. Finally, our trial, unlike the ELCA registries, included a routinely measured serum creatine kinase band level after each procedure.

A comparison of our balloon angioplasty group with randomised trials of balloon angioplasty shows similar results with respect to the clinical event rate and complication rate.[23–26] However, there was a marked difference in our study in the procedural dissection rate observed in both treatment groups. The high incidence of dissections in our study might be related to selection of more complex coronary lesions compared with the other studies.[5] Although the incidence of dissections was high, the majority of dissections were type A, B, or C, which are benign.

The serum level of the creatine kinase myocardial band was systematically assessed in our trial. In this respect, the periprocedural myocardial infarction rate (3·2%), including Q and non-Q-wave myocardial infarctions, cannot be compared with randomised balloon angioplasty studies. The incidence of myocardial infarctions is low compared with other studies in which the serum creatine kinase myocardial band level was evaluated after intracoronary interventions. These studies reported substantial increases in enzymes in 10–20% of procedures after balloon angioplasty or after application of other new devices such as directional atherectomy or coronary stenting.[27,28]

This first randomised clinical trial of ELCA versus balloon angioplasty in obstructive coronary artery disease demonstrated no additional benefit of ELCA. Consequently, is there a role for ELCA in the treatment of coronary lesions? It is important to mention that the additional cost of ELCA favours the use of other treatments. Several modifications of the current laser technique are under investigation to optimise the results of intracoronary laser angioplasty. Adjustments in laser techniques to reduce formation of fast expanding and imploding vapour bubbles include a flushing protocol,[29] application of sequential laser fibre activation,[30] use of lower energy fluence,[31] and use of a new laser catheter design in which homogeneous light distribution is provided.

The results of this trial demonstrate no additional benefit of ELCA over balloon angioplasty with the current laser technique.

Institutions participating in the AMRO study (number of patients enrolled): Academic Medical Center, University of Amsterdam, Netherlands (144); Thorax Center, Rotterdam, Netherlands (99); Catharina Hospital, Eindhoven, Netherlands (57); and Miami Heart Institute, Miami, Florida, USA (13).

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Safety monitoring committee: A Algra, C Borst, A V G Bruschke.

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Original Contribution

Angiopeptin-Eluting Stents: Observations in Human Vessels and Pig Coronary Arteries

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Local drug delivery from polymer-coated coronary stents may reduce the incidence of in-stent restenosis. Angiopeptin, an inhibitor of smooth muscle cell proliferation, may reduce the clinical impact of restenosis. The objectives of this study were to characterize the release kinetics and distribution of angiopeptin-loaded phosphorylcholine (PC)-coated drug delivery (DD) Bio*divYsio* stents and assess their safety and efficacy at reducing neointima formation. I^{125}-angiopeptin-loaded DD-PC-coated stents were implanted into human saphenous vein segments *ex vivo*, and I^{125} angiopeptin was detected in the medial layer at 1 hour. When implanted in pig coronary arteries, I^{125} angiopeptin was found adjacent to the stent at intervals up to 28 days. No significant amounts were found elsewhere. To assess efficacy, twelve angiopeptin-loaded DD-PC-coated stents, twelve non-loaded DD-PC stents, ten standard PC-coated stents and 8 uncoated stents were implanted into normal porcine coronary arteries. Stents were harvested at 28 days and neointima formation was assessed by computerized morphometry. No adverse tissue reactions were seen with any of the PC-coated stents. No significant differences were seen in neointimal or luminal cross-sectional areas between study groups. Local delivery of I^{125} angiopeptin into the vascular wall can be achieved using a PC-coated stent. Delivery of angiopeptin from "drug delivery" PC-coated stents is safe, but does not lead to a significant reduction in neointimal growth at 28 days within the parameters of this study.

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Coronary stenting is generally associated with lower rates of restenosis than balloon angioplasty.[1,2] However, in-stent restenosis (ISR) remains a significant clinical problem.[3] Pharmacological inhibition of ISR has shown potential in laboratory animals, but has not been associated with clinical benefit in large randomized clinical trials in man.[4,5] Local drug delivery is an attractive proposition, but delivery catheter devices are inconvenient, may cause further injury to the vessel wall, and result in inefficient delivery and regional rather than local distribution.[6-11] Therefore, there has been much recent interest in the use of drug eluting stents.[12-16]

Angiopeptin, a synthetic analogue of somatostatin, has been shown to reduce neointima formation after balloon injury when given systemically in some animal models,[17,18] and to reduce adverse events in a clinical trial.[19] However, the drug is rapidly degraded by the liver[20] and therefore local delivery strategies have been attempted.[21] Angiopeptin-loaded stents reduced luminal narrowing in a pig model of in-stent stenosis compared to non-loaded stents, although the effect observed was due to inhibition of myointimal proliferation arising as a consequence of the poly(organo)phosphazene stent coating.[22]

The Bio*divYsio* drug delivery stent (Biocompatibles Ltd., Farnham, United Kingdom) is a stainless-steel, balloon-expandable stent coated with a phosphorylcholine (PC) polymer. PC occurs naturally on the external surface of cell membrane lipid bilayers. PC coating confers hemocompatibility,[23-25] and can act as a drug reservoir, capable of controlled release. PC is stable in saline and ethanol (Terry Vick, unpublished observations, 1999), and the durability of the PC coating has been demonstrated using atomic force microscopy following implantation into pig coronary arteries for periods up to 6 months.[26]

The aims of the present study were: 1) to determine the release of I^{125} angiopeptin from PC-coated stents into human saphenous vein *ex vivo*, and pig coronary arteries *in vivo*; and 2) to investigate the safety and efficacy of angiopeptin-loaded PC-coated stents in porcine coronary restenosis.

METHODS

Stent preparation

BiodivYsio PC-coated stents were used. The thickness of the PC coating for the *ex vivo* studies was 100 nm on both the luminal and abluminal aspects of the stent. Following initial *ex vivo* experiments (see below), the thickness of the PC coating on the abluminal aspect of the stents was increased to 1 μm ("drug delivery" PC-coated stent, or DD-PC), allowing for greater loading of angiopeptin. I^{125} angiopeptin (prepared by Nycomed Amersham Imaging, Princeton, New Jersey) was used for assessment of release characteristics. Stents were placed into I^{125} angiopeptin solution, incubated for 30 minutes at 37 °C, and dried at 40 °C for 1 hour. The level of radioactivity per stent was quantified using a gamma counter (Wallac Compugamma, Perkin Elmor, Connecticut) and the amount of angiopeptin loaded, calculated with reference to a 500 μg standard, was 3.9 ± 0.4 μg for *ex vivo* studies and 8.32 ± 0.8 μg for *in vivo* delivery studies. Angiopeptin (generic, Lanreotide; kindly provided by Beaufour Ipsen, United Kingdom) was used for safety and efficacy studies. Balloon-mounted DD-PC stents were dipped into a 10 mg/ml solution of angiopeptin in 100% ethanol as described above, and an additional 20 μl of angiopeptin solution was applied directly to the stent surface using a pipette tip following the drying step to increase loading. High-performance liquid chromatography (HPLC) was used to determine angiopeptin loading. Angiopeptin was eluted from a Vydac C18 HPLC column with acetonitrile/sodium perchlorate mobile phase at a flow rate of 1 ml/minute and monitored at 280 nm with an ultraviolet detector. An average loading of 126 μg of angiopeptin was achieved per stent used for the safety and efficacy study.

Release and delivery of I^{125} angiopeptin from PC-coated stents

***Ex vivo* studies in human saphenous vein.** The I^{125} angiopeptin-loaded stents were deployed using a 3.5 x 20 mm PTCA balloon (Bard Corporation, Billerica, Massachusetts) into segments of human saphenous vein obtained from patients undergoing coronary artery bypass grafting (n = 6). The protocol was approved by the Northern General Hospital Ethics Committee and specimens were collected following informed patient consent. The vein and stent were then washed in 10 ml of HEPES-buffered RPMI 1640 culture medium (LIFE, Paisley, United Kingdom) supplemented with penicillin (100 μl/ml), streptomycin (100 units/ml) and glutamine (2 mmol/L) (all from ICN Flow labs) for 10 seconds. The vein was secured in an organ culture chamber and perfused at physiological pressure and flow rates with 100 ml culture medium using a peristaltic pump for either 1 or 24 hours (n = 3 at each time point). At the end of each experiment the vein was cut from the chamber, opened longitudinally to remove the stent, and divided into proximal, stented and distal segments. Tissue samples and the explanted stent were counted for the amount of radioactivity present using a gamma counter. All counts were adjusted for radioactive decay (I^{125} half life = 60 days).

***In vivo* studies in porcine coronary arteries.**

Surgical procedures and stent implantation. All animal procedures were conducted according to United Kingdom Home Office Regulations. The investigation conforms with the guide for the care and use of laboratory animals published by the United States National Institute of Health (NIH publication no. 85-23, revised 1996). Yorkshire pigs weighing 16–20 kg were given aspirin (150 mg) preoperatively and for up to 5 days. General anesthesia was induced and coronary angiography was performed as previously described.[17] I^{125} angiopeptin-loaded PC-coated stents were mounted onto 3.5 mm coronary angioplasty balloons with minimal handling and deployed at 8 atm in 1 segment of left anterior descending coronary artery, 2.8 mm diameter by quantitative angiography, achieving a mid-stent stent:artery ratio of 1.25:1. The animals (n = 8) were killed at 1 hour, 24 hours, 7 days and 28 days (2 animals at each time point). Non-radio-labelled angiopeptin-loaded stents (n = 8) were implanted into coronary arteries of 4 additional animals that were subsequently killed at 1 hour, 7 days and 28 days, prior to analysis of angiopeptin by HPLC.

Measurement of surface radioactivity. A Geiger counter (Scintillation meter type 5.40, Mini Instruments, Ltd., Essex, United Kingdom) was used to record over-the-skin radioactivity at 5-minute intervals for the first 25 minutes following stent deployment and immediately before sacrifice. Measurements were taken over the heart, abdomen, kidney, head, leg muscles and bladder.

Detection of I^{125} angiopeptin in blood, urine and tissue samples. Arterial blood samples were obtained immediately before and after each stent deployment, at 5 and 30 minutes following stent deployment and when the animal was killed. One blood sample was also collected from the delivery sheath immediately after stent deployment. Urine and tissue samples were obtained immediately after sacrifice of the animal. Tissue samples were taken from skeletal muscle, cartilage, small intestine, thyroid gland, lung, liver, spleen, kidney, skin, aorta, right and left atria, right and left ventricles, pericardium, left anterior descending (LAD), right coronary (RCA) and circumflex coronary arteries, and myocardium from beneath the stent. The stented coronary arteries were divided into stented, proximal and distal regions. The stented segment was cut longitudinally to remove the stent, with the exception of the 28-day stents, which were left *in situ* because of encasement in neointima. Tissue samples were weighed and counted with a gamma counter as described above. In

addition, formalin-fixed paraffin sections were prepared for microautoradiography by dipping in photographic emulsion (Hypercoat LM-1, Amersham) and exposed at 4 °C for 11 weeks. For 28 day experiments, stented arteries were formalin-fixed, processed and embedded in T8100 resin (Taab Laboratories, Berkshire, United Kingdom) and transverse sections of vessel with stent *in situ* were cut and polished[18] for autoradiography.

HPLC analysis of angiopeptin. Following stent removal, tissue lysates were prepared and HPLC analyses were performed, as described above. Angiopeptin remaining on the explanted stents was eluted with ethanol and also subjected to HPLC analysis.

Safety and efficacy of angiopeptin delivery from DD-PC-coated stents

Study protocol. Stents were deployed as described, this time using both RCA and LAD in each animal. Five thousand units of sodium heparin were given at the start of catheterization. The animals were killed at 28 days and the arterial segments with stents *in situ* were excised and immersion-fixed in formalin for 24 hours, processed and embedded in T8100 resin (Taab Laboratories) and transverse sections were cut for histology. There were 4 study groups: angiopeptin-loaded DD-PC coated stents (12 arteries, 6 pigs); DD-PC control stents (12 arteries, 6 pigs); standard (non-DD) PC-coated BiodivYsio stents (10 arteries, 5 pigs); and uncoated DivYsio stents (8 arteries, 4 pigs).

Morphometrical analysis. Of 12–20 sections per stent, three were randomly selected (1 from each of the proximal, middle and distal segments of the stent). Sections were discarded if they were incomplete or distorted. These were analyzed by semi-automated quantitative morphometry (Lucia Image Analysis software, Nikon, United Kingdom). The lumen, neointima and total vessel cross-sectional areas were measured and recorded. A cumulative injury score (a modification of the Schwartz Score),[19] to reflect mild and moderate arterial injury, was used. Each strut was scored: 0 = no imprint on vessel wall; 1 = internal elastic lamina deformed < 45°; 2 = internal elastic lamina deformed > 45°; 3 = internal elastic lamina broken; and 4 = external elastic lamina broken. The injury score for each section was calculated as the sum of the scores for each strut. To correct for the amount of injury and vessel size, each measurement was divided by the vessel area of that section and then by the injury score. This value was then multiplied by 10^4 to give an integer of arbitrary units.

Statistics

All descriptive statistics are expressed as mean ± the standard error of the mean. Morphometrical data in the efficacy study were analyzed using a 1-way ANOVA. The level of significance was taken as $p < 0.05$.

Table 1. Tissue concentrations of I^{125} angiopeptin in human saphenous vein following deployment of drug-loaded stents: I^{125} angiopeptin concentration ng/mg wet weight of tissue (± standard error of mean)

Tissue Segment	1 Hour	24 Hours
Proximal	1.75 ± 0.4	1.4 ± 0.4
Stented	2.57 ± 0.4	1.24 ± 0.4
Distal	0.38 ± 0.05	0.83 ± 0.2

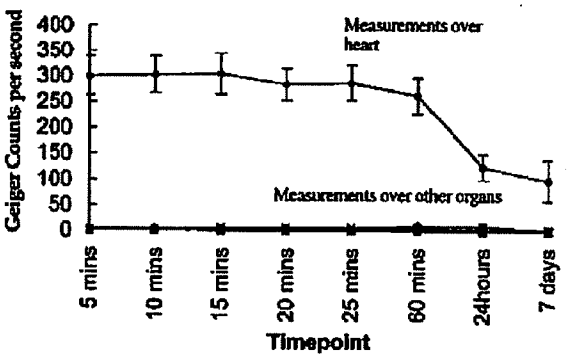


Figure 1. *Surface distribution of gamma radiation (Geiger counts per second) following stent deployment. Error bars represent standard error of the mean.*

RESULTS

Release and delivery of I^{125} angiopeptin from PC-coated stents

***Ex vivo* studies in human saphenous vein.** I^{125} angiopeptin was detected in all tissue and culture medium samples at both 1 and 24 hours (Table 1). At 1 hour, 7.5 ± 0.5%, and at 24 hours, 2.66 ± 0.7% of the initial loading was detected in the stented region of vein. The total dose detected within the vessel wall, including proximal, stented and distal regions, was 0.38 ± 0.07 µg (13.9% of the initial dose) at 1 hour and 0.22 ± 0.05 µg (7.4% of initial dose) at 24 hours.

***In vivo* porcine coronary artery studies.** The surface distribution of gamma radiation over the heart immediately following stent deployment was approximately 20-fold greater than for the other organs, which were approximately at background levels (Figure 1). At 28 days, quantitative surface readings were not comparable with baseline levels due to growth of the animal, but radioactivity was still detected (12.5 ± 2.5 cps).

The level of I^{125} angiopeptin collected from within the delivery catheter following stent deployment was 30.4 ± 8.6 ng/ml. The systemic blood level 5 minutes after stent deployment was 0.35 ± 0.08 ng/ml; this level reduced until no radioactivity was detected in the blood at 7 and 28 days. The level of I^{125} angiopeptin in urine was 0.32 ± 0.29 ng/ml at 1 hour and 0.01 ± 0.01 ng/ml at 28 days.

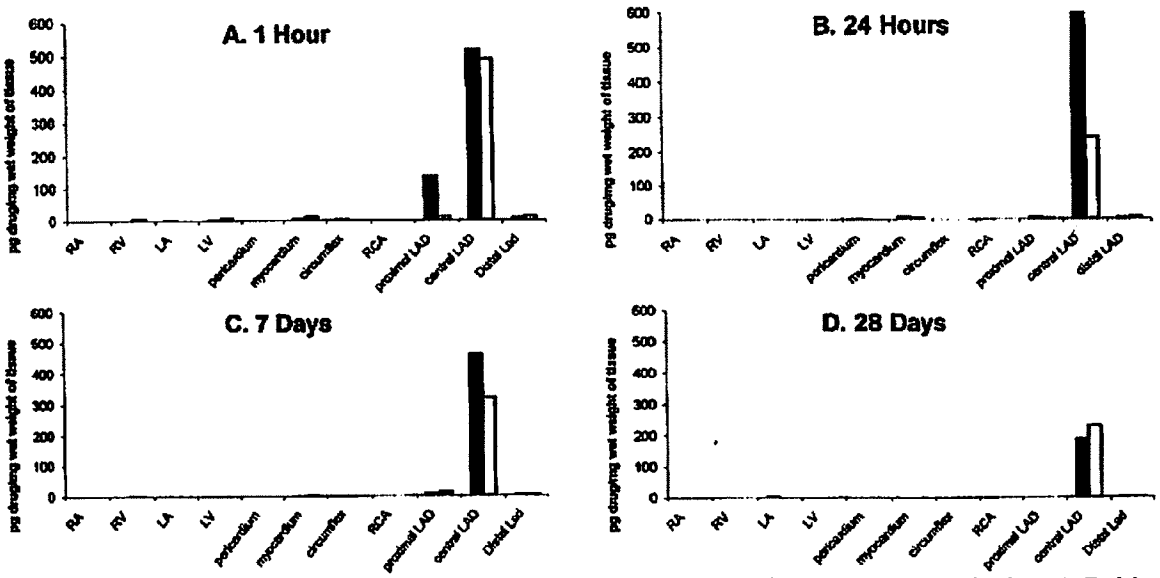


Figure 2. *Tissue concentrations of I^{125} angiopeptin after placement of I^{125} angiopeptin-loaded stents (pg/mg wet weight of tissue). Each bar represents a separate experiment in one pig.*

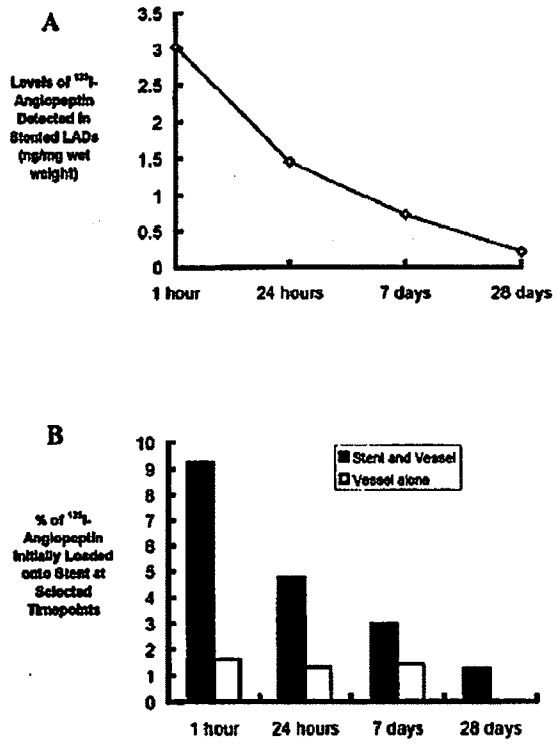


Figure 3. *(A) Concentrations of I^{125} angiopeptin detected in the stented left anterior descending (LAD) coronary artery (stent and artery combined) at various time points following implantation. (B) Amounts of I^{125} angiopeptin detected in the stented LAD expressed as percentages of initial total I^{125} angiopeptin loading. In 28-day experiments, the stent and vessel were quantified together. Data are the average values from two pigs for each time point.*

Maximum levels of I^{125} angiopeptin within the heart were detected in the wall of the left coronary artery directly surrounding the stent (Figure 2). I^{125} angiopeptin was also identified within the proximal and distal regions of the left coronary artery. Low levels of I^{125} angiopeptin were detected in the unstented circumflex and right coronary arteries at all time points. The amount of I^{125} angiopeptin detected in the stented LAD (stent and artery combined because of encasement in neointima) decreased by 50% over the first 24 hours and then continued to decrease up to 28 days (Figure 3).

The distribution of I^{125} angiopeptin within the vessel wall was investigated by microautoradiography and was observed along the luminal surface, extending a short distance into the media of the vessel around the stent at 1 hour (Figure 4), 24 hours and 7 days. I^{125} angiopeptin was seen in patches along the intima, corresponding to the location of the stent struts prior to their removal, and these regions of radioactivity at 28 days were also seen on X-ray film autoradiographs (Figure 5).

HPLC analysis confirmed that the angiopeptin was intact in arterial tissue at 1 hour and 7 days following stent implantation *in vivo* (data not shown). Angiopeptin eluted from stents after 1 hour, 7 days and 28 days *in vivo* was also shown to be intact by HPLC.

Safety and efficacy of angiopeptin delivery from PC-coated stents

At 28 days, histology revealed complete stent occlusion in 2/12 stents in the DD-PC control group. These stents were associated with very high injury scores. There were no occlusions with the angiopeptin-loaded DD-PC, standard PC and uncoated stent groups.

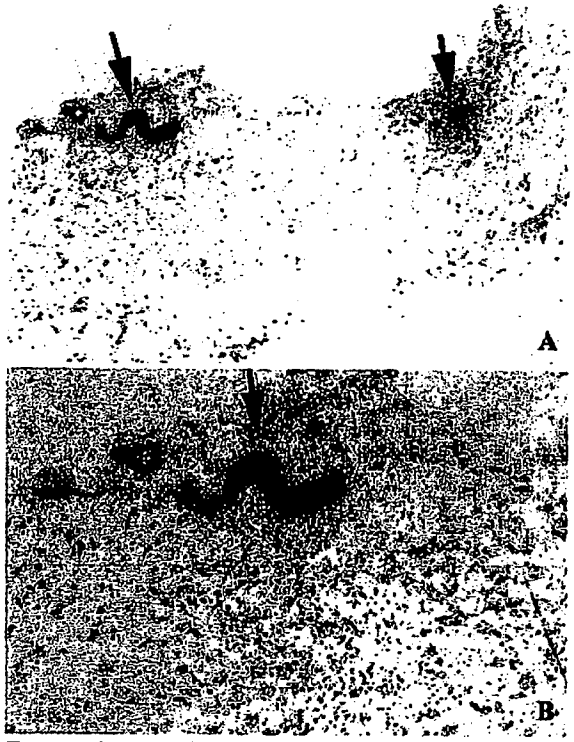


Figure 4. *Location of I^{125} angiopeptin delivered to porcine coronary arteries in vivo. Microautoradiographs show the presence of I^{125} angiopeptin (arrowheads) in porcine coronary artery at 7 days (B = high power of A). (A) Original magnification 32x and (B) 64x.*

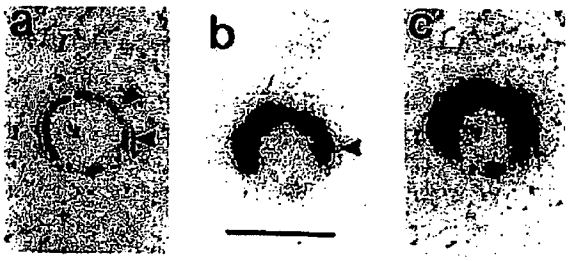


Figure 5. *Transverse sections of porcine coronary artery at 28 days following implantation of I^{125} angiopeptin-loaded stents. (A) Photograph of transverse section of coronary artery showing location of stent struts (arrowheads). (B) Autoradiograph showing location of I^{125} angiopeptin surrounding region of stent struts (arrowhead). (C) Autoradiograph B superimposed on transverse section A confirming location of I^{125} angiopeptin. Scale bar represents 5 mm.*

The injury score, vessel size, neointimal and luminal cross-sectional area (corrected and uncorrected for injury score and vessel size) for all 4 groups of stents are shown in Table 2. No significant differences were seen in neointima formation between the different groups (Figure 6).

DISCUSSION

We have shown that I^{125} angiopeptin can be loaded onto DD-PC coated stents, can be detected in human vessels 1 and 24 hours following stent deployment *ex vivo*, and can be detected *in vivo* in pig coronary arteries up to 28 days after stent deployment. Furthermore, sustained, high, local arterial wall concentrations of drug, compared to levels in systemic blood or other organs, can be achieved via stent-based delivery. This study has also demonstrated that angiopeptin, delivered from the DD-PC BiodivYsio stent, is safe and not associated with any adverse biological reaction. In this dose, with this formulation, and using this delivery system, angiopeptin does not reduce in-stent restenosis compared with uncoated, standard PC-coated or DD-PC coated stents. It is possible that efficacy may be achieved by judicious improvements in drug loading, release kinetics and stent design. The study also shows that DD-PC coating, like standard PC, is biologically neutral.

The tissue level of angiopeptin required for a significant biological effect is unknown, but in this study we achieved significantly higher concentrations than a similar investigation that reported a positive biological effect.[22] Hong et al.[21] demonstrated a decrease in neointimal hyperplasia in the pig with plasma levels of angiopeptin of 50 pg/ml, but tissue levels were not determined.

The degree of injury produced by stent implantation was relatively mild compared to that in other studies,[18,22] where more extensive neointima was seen and a beneficial effect of angiopeptin was observed; it could be that differences are less likely to be seen in these circumstances. The reduction in clinical events following balloon injury, without a significant reduction in restenosis, in a clinical trial of systemically administered angiopeptin,[19] may have been due to improved vasodilatory responses of the vessel wall.[30] Also, previous studies have demonstrated a loss of effect if angiopeptin was not given prior to the procedure,[17] possibly due to the long half-life of growth factors such as IGF-1, which angiopeptin is thought to inhibit. No pretreatment was given in this study. In addition, after initial wash-out, insufficient drug for a therapeutic effect might have remained on the stent to be released into the vessel wall; however, the tissue concentration detected was over 100-fold that seen in the study of De Scheerder et al. at 7 days after stenting.[22] Also, in that study, the reduction seen with angiopeptin was observed in an exceptionally thick neointima, thought by the authors to have been induced by the polyphosphazene polymer coating.

Recent investigations into Sirolimus eluting stents in human coronary arteries have shown excellent results in inhibiting restenosis.[15,31] In addition, clinical trials of other drug-loaded stents are underway, including paclitaxel, actinomycin D and c-myc antisense. The success with Sirolimus is therefore a stimulus to further improve stent-based drug delivery technology and to identify new targets for inhibiting restenosis.

Comparison of drug delivery technologies

The use of catheter-based drug delivery devices is restricted by inconvenience, potential for damage to the

Table 2. Morphometrical analysis of porcine coronary arteries 28 days after stent deployment

Stent Coating	Injury Score	Vessel Size (CSA in mm²)	Neointima (CSA in mm²)	Neointima (Corrected)	Lumen (mm²)	Lumen (Corrected)
Lanreotide-DD-PC	18.9 ± 1.4	9.91 ± 0.18	2.78 ± 0.22	157 ± 10	3.41 ± 0.28	241 ± 36
DD-PC	23.2 ± 2.6	9.03 ± 0.30	3.70 ± 0.38	187 ± 14	2.47 ± 0.27	223 ± 38
Standard PC	17.4 ± 0.6	8.2 ± 0.28	2.06 ± 0.23	154 ± 24	3.95 ± 0.28	268 ± 29
Uncoated	20.4 ± 1.6	9.71 ± 0.33	2.73 ± 0.34	138 ± 14	4.44 ± 0.39	270 ± 31

All values are given as mean ± SEM; CSA = cross-sectional area; Corrected values refer to cross-sectional area in mm² divided by injury score and vessel area, and multiplied by 10^4; Standard PC coating consists of 100 nm of PC on both luminal and mural aspects of the stent. DD-PC refers to a thicker coating (1 μm) of PC on the mural aspect only of the stent

vessel wall due to the injection of fluid volume and rapid wash-out. Furthermore, data from our own and other groups have demonstrated low efficiency of catheter-based delivery,[9–11] and delivery from such devices is more regional than local.[10] In the present study, the percentage of initial I^{125} angiopeptin loaded and subsequently detected in the stented artery was 9.25% at 1 hour, falling to 1.25% at 28 days. The amount detected within the vessel alone at 1 hour, 24 hours and 7 days remained fairly constant at 1.6–1.4% of the initial amount of I^{125} angiopeptin loaded onto the stent.

Local delivery of dexamethasone via a polylactic acid polymer-coated stent into porcine coronary arteries achieved sustained local concentration for at least 28 days,[32] although neointimal hyperplasia was not reduced. A similar dexamethasone polymer-coated stent in canine femoral arteries showed a significant reduction in neointima at 3 weeks.[33] Forskolin, delivered via a polyurethane-coated, removable stent, was present at high levels within rabbit carotid arteries relative to blood and other organs for up to 24 hours.[34,35] Our observation of sustained, high, local arterial wall concentrations of drug compared to levels in systemic blood or other organs confirms efficient local drug delivery from a coated stent.

Phosphorylcholine versus alternative polymers

In this study, angiopeptin was absorbed into the PC coating without covalent or ionic bonding. This results in a concentration gradient of loading, with more on the outside of the coating, and explains the high early release of I^{125} angiopeptin detected in the catheter flush. By controlling the cross-linked density, water content, isoelectric point and other characteristics, the PC-coating could be tailored to achieve improved loading, release and less early wash-off of drug. The advantage of PC is that it does not elicit an inflammatory response.[36] This is in contrast to other polymers,[37] and has been further confirmed in the present study.

Angiopeptin as an anti-restenotic agent

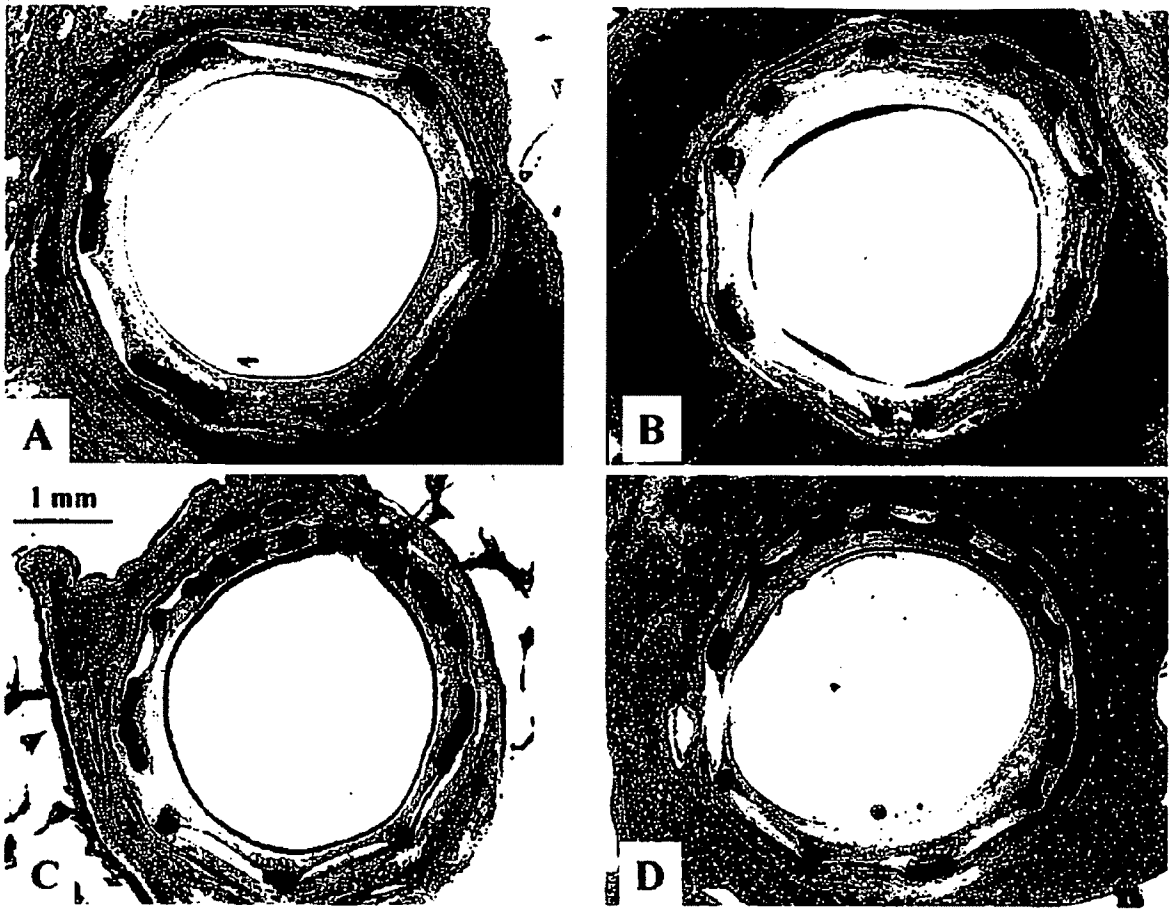
The mechanism of action of angiopeptin is not fully understood. It has been postulated that the effects of angiopeptin are mediated through its ability to inhibit pituitary growth hormone release and decrease insulin-like growth factor 1 (IGF-1) in the vessel wall following balloon injury.[38,39] However, all somatostatin analogues inhibit growth hormone release, but not all inhibit intimal hyperplasia, suggesting that angiopeptin's effect on smooth muscle cell proliferation may not be due to effects on the pituitary.[40] Foegh et al.[17] noted a lack of effect by angiopeptin if administration is delayed for 1 hour after injury. In addition, angiopeptin administration following balloon injury significantly reduces the expression of the early response genes c-*fos* and c-*jun*, believed to have a role in vascular cell proliferation and apoptosis.[41] Somatostatin analogues, including angiopeptin, activate membrane-bound phosphatases,[42] which may be responsible for inactivating tyrosine kinase receptors for growth factors such as IGF-1 and PDGF.[43] Thus, it appears that angiopeptin may work through a local mechanism in the vessel wall, and may therefore be more suitable for local delivery than systemic delivery.

Study limitations.

The *ex vivo* model is a recirculating system, with a total volume of 100 ml, which may have affected the diffusion properties of angiopeptin. Dynamic metabolism and excretion of angiopeptin are also absent in this model. However, the pharmacokinetics of the *in vivo* system are likely to have been more realistic. Human saphenous vein has been used in our *ex vivo* studies. Although many structural and functional differences exist between arteries and veins, human saphenous vein is appropriately sized and readily available compared to human artery, and is clinically relevant in the stenting of saphenous vein grafts. Most importantly, we have shown that PC-coated stents are capable of delivering angiopeptin to human vascular tissue. The *in vivo* efficacy studies lacked randomization in that each of the control group procedures were performed first, followed by the angiopeptin treatment group. Non-diseased, juvenile pig arteries were also used. However, this model has often been used in studies to determine efficacy.

CONCLUSION

We have shown that local delivery of I^{125} angiopeptin into both human vessels *ex vivo* and in pig coronary



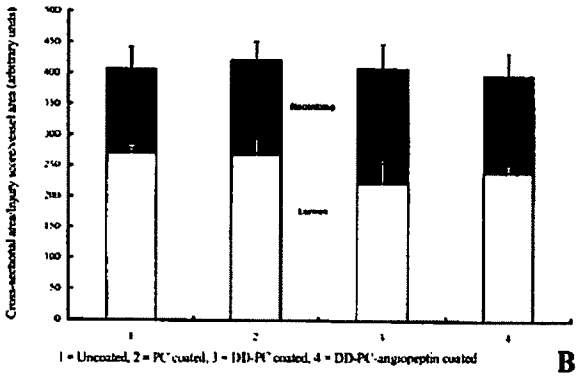


Figure 6. *Vessel morphometry after deployment of different DivYsio stents.* **(A)** *Photomicrographs of stented porcine coronary artery cross-sections (original magnification x 2). A = DD-PC-Lanreotide; B = DD-PC; C = standard PC; D = uncoated DivYsio stent.* **(B)** *Bar chart to demonstrate neointimal (closed bar) and luminal (open bar) cross-sectional areas of porcine coronary arteries (corrected for injury score and vessel size) implanted with DD-PC-Lanreotide, DD-PC, standard PC or uncoated DivYsio stents. Error bars represent standard error of the mean, values are arbitrary.*

arteries *in vivo* can be achieved via angiopeptin-eluting PC-coated stents. This study has also demonstrated that angiopeptin, delivered from the DD-PC BiodivYsio stent (with a polymer coating ten times thicker than the standard PC coating) is safe and is not associated with any adverse biological reactions. These results provide a basis for further research using the DD-PC stents.

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Original Article

In-stent Restenosis. Acute and Long-Term Outcomes after Excimer Laser Coronary Angioplasty

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Objective – *With the increased use of intracoronary stents, in-stent restenosis has become a clinically significant drawback in invasive cardiology. We retrospectively assessed the short- and long-term outcomes after excimer laser coronary angioplasty of in-stent restenosis.*

Methods - *Twenty-five patients with 33 incidents of in-stent restenosis treated with excimer laser coronary angioplasty (ELCA) were analyzed. Sixty-six percent were males, mean age of 73±11 years, and 83% were functional class III-IV (NYHA). ELCA was performed using 23 concentric and 10 eccentric catheters with a diameter of 1.6-2.2 mm, followed by balloon angioplasty (PTCA) and ultrasound monitoring. The procedure was performed in the following vessels: left anterior descending artery, 10; left circumflex artery, 8; right coronary artery, 6; left main coronary artery, 2; and venous bypass graft, 7.*

Results – *The ELCA was successful in 71% of the cases, and PTCA was 100% successful. The diameter of the treated vessels was 3.44±0.5mm; the minimal luminal diameter (MLD) increased from 0.30mm pre-ELCA to 1.97mm post-ELCA, and to 2.94mm post-PTCA (p<0.001). The percent stenosis was reduced from 91.4±9.5% before ELCA to 42.3±14.9% after ELCA and to 14.6 ± 9.3% after PTCA (p<0.001). Seventeen (68%) patients were asymptomatic at 6 months and 15 (60%) at 1 year. New restenosis rates were 8/33 (24.2%) at 6 months and 9/33 (27.3%) at 12 months.*

Conclusion - *ELCA is safe and effective for the treatment of in-stent restenosis. In the present sample, a slight increase in new restenotic lesions between 6 and 12 months was found.*

Key-words: laser, restenosis, stents

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Coronary heart disease remains a major cause of morbidity and mortality during the most productive years of life. Currently, a series of therapeutic options are available to manage this condition, which develops as a result of well-known risk factors. In addition, prevention and medical therapy represent the mainstay in the management of this disease. However, myocardial revascularization with saphenous vein grafts or anastomoses of the internal thoracic arteries and, ultimately, balloon coronary angioplasty, constitute the most recent therapeutic developments in cases where the symptoms persist. Among the new invasive techniques, coronary stenting currently represents the most frequently employed therapeutic modality. The rate of coronary restenosis is higher with stenting than that found with balloon angioplasty[1,2] as a significant number of patients suffer from in-stent restenosis[3-6].

The excimer laser (LASER) has been used in the treatment of complex lesions[7,8]. it makes the treatment of in-stent restenosis easier and its results in restenosis are possibly better than those found with balloon angioplasty. We examined this therapeutic modality to define the role of LASER in in-stent restenosis and to assess the early and late outcomes.

Methods

The first 25 patients with 33 instances of in-stent restenosis treated with LASER were assessed. Patients with acute myocardial infarction (AMI) or cardiogenic shock were excluded. The clinical features of the patients are summarized in table I. The angiographic analysis was performed with an off-line quantitative method.

After the clinical evaluation, all patients were reassessed in order to identify the angiographic restenosis and the functional class. A successful procedure was defined as the presence of a residual lesion <50% in the absence of a new procedure, AMI, emergency surgery or death. The LASER was considered successful when a reduction ≥20% of the initial stenosis was noted; a new angiographic restenosis was defined as the presence of an obstruction ≥50% in the treated site at any time during the follow-up; and AMI was defined as levels of CK and CK-MB above the normal range.

Table I – Clinical features of individuals with in-stent restenosis (%) (n=25)	
Age (years)	73± 11
Gender (males)	66
Class III-IV	83
Previous infarction	51
Previous heart surgery	57
Ejection fraction	48±9
Hypercholesterolemia	89
High blood pressure	63
Family history	50
Diabetes mellitus	31
Smokers	23

Before the procedure, all patients signed an informed consent, according to the guidelines of the Geneva Convention, the Food and Drug Administration (FDA) and the institution's regulatory committee for research. Twenty-four (73%) lesions were treated with a single stent and 9 (27%) with multiple stents. Ultrasound was employed to assess and optimize the final angiographic outcome and additional inflations were performed, when required. With regard to the treated vessels (fig. 1), 20 (61%) belonged to the left system, 6 (18%) to the right system, and 7 (21%) were saphenous vein bypass grafts.

Laser therapy was performed according to the standard technique [4]. The CVX-300 generator (Spectranetics Corporation, Colorado Springs, Colorado), which works with a wavelength of 308nm, a laser fluency of 30-60mJ/mm² and a pulse duration of 135ns emitted at a repetition rate of 25Hz, was used as the source of energy. The over-the-wire catheters had a diameter of 1.4mm (n=2), 1.7mm (n=16), 2.0mm (n=17), and 2.2mm (n=3) to manage lesions in vessels with a diameter of 3.44±0.5 mm.

Results

The reference diameter of the vessel (RDV) was 3.44±0.5mm. The stents that showed restenosis were: Palmaz Schatz, 23; CRI, 6; CRII, 1; J & J Biliar, 3; Wallstent, 4; and AVE, 2 (table II). In regard to the number of stents per each lesion treated, 24 (73.0%) had a single stent placed and 9 (27.0%) had multiple stents placed. In regard to the diameter of the vessels treated, in 25/39 (64.1%) of them it was 3.5mm, in 10/39 (25.6%) it was 4.0mm, in 3/39 (7.7%) it was 3.0mm and in 1/39 (2.6%) it was 5mm. Of the lesions treated, 100% were complex (eccentric and long). The MLD increased from 0.3mm before the procedure to 1.97mm after the LASER and to 2.94mm at the end of the procedure, as assessed by off-line quantitative angiography (fig. 2). The stenosis, which in the beginning was 91.4±9.5%, was reduced to 42.3±14.9% after the LASER and to 14.6±9.3% at the end of the procedure (fig. 3). The LASER was 71% successful and the PTCA, 100% successful (fig. 4). No acute complications of any kind were noted. At 6 months, 17/25 (68%) patients were asymptomatic and, at 1 year, 15/25 (60%) were asymptomatic. Of the 33 lesions, 8 (24%) required a new procedure at 6 months and 9 (27%) at 1 year.

No differences during the 6-month or 1-year follow-up were noted with regard to emergency surgery and death. None of the patients had an AMI at 6 months or 1 year of

Table II - Stents with restenosis treated with LASER	
Stent	#
Palmaz-Schatz	23
Gianturco-Roubin I	7
J & J Biliar	3
Wallstent	4
Microstent	2

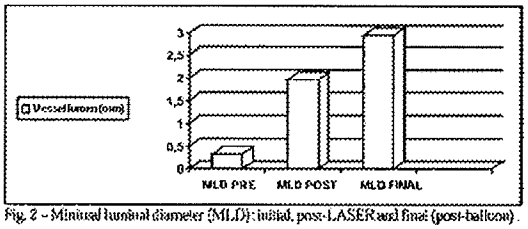

Fig. 2 – Minimal luminal diameter (MLD): initial, post-LASER and final (post-balloon).

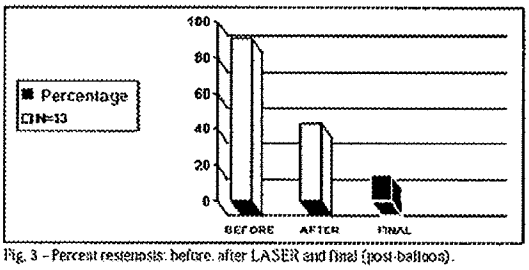

Fig. 3 – Percent restenosis: before, after LASER and final (post-balloon).

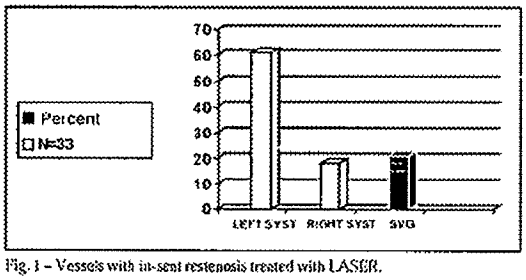

Fig. 1 – Vessels with in-sent restenosis treated with LASER.

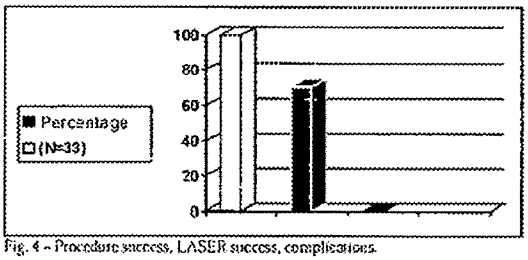

Fig. 4 – Procedure success, LASER success, complications.

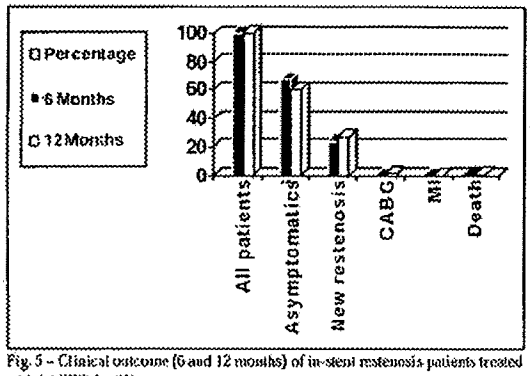

Fig. 5 – Clinical outcome (6 and 12 months) of in-stent restenosis patients treated with LASER (n=25).

follow-up (fig. 5). One (4%) patient underwent elective heart surgery between 6 and 12 months of follow-up, and another patient (4%) died of a noncardiac cause in the first 6 months of follow-up.

Discussion

The present study examines a group of patients of both sexes, most of whom had severe myocardial ischemia. Although more than half of these patients had previously suffered a myocardial infarction and undergone coronary artery bypass surgery, all had excellent ventricular function.

This factor may have partially accounted for the absence of acute clinical complications. It is of note that most patients had hypercholesterolemia and high blood pressure and that the low number of smokers in this series reflects the results of the nonsmoking laws and campaigns that take place in the United States. A recent study suggests that diabetes mellitus, multiple stents and a lower MLD after stenting could be the predictive factors of restenosis [9]. One of the main uses of LASER angioplasty is in treating long lesions [7,8]. The management of in-stent restenosis with balloon [10,11], Simpson atherectomy catheter [12,13], rotablator [14-16] or with the placement of a new stent [17,18], although effective and relatively safe, has been disappointing. The late permeability after treatment with the above-mentioned devices relates to a rate of restenosis of approximately 40% by the 6th month of follow-up. In-stent restenosis presents as a long lesion, because the endothelial neoformation lines the entire internal surface of the stent, and is exacerbated by multiple stenting [19-21]. The ability of the LASER in performing tissue ablation has been previously shown in long lesions [7,8]. The studies of treatment of in-stent restenosis with LASER are limited. In a study of 7 cases, the procedure was considered effective and safe, and intracoronary monitoring with ultrasound showed that the LASER does not reach the stent [20]. In a recent retrospective nonrandomized study [22], the procedure was 98% successful, with a mortality rate of 2% and a rate of emergency surgery of 11%. The new restenosis rate at 6 months was 21% for laser + balloon and 38% for the balloon. Our study assesses patients with in-stent restenosis treated with laser + balloon. The procedure was 100% successful and the LASER was 71% successful. At 6 months, the rate of new restenosis was 24.2%, and the rate of a new procedure in the target vessel (including a patient who underwent emergency surgery) was 27.3%. One patient died from a noncardiac cause. It is of note that the results in this subgroup, although a smaller sample, are similar to the previously mentioned series. The rates of new restenosis in the present study may also be related to the diameter of the vessels treated, as 89.7% had a diameter ≥3.5mm. Similarly, it is not known if the rate of new restenosis at 6 months will remain the same as at 12 months, or if it will increase, considering the effect of the stent, a foreign body, within the vessel. Later, the rate of new restenosis was shown to increase from 24.2% to 27.3%, and the rate of a new procedure in the vessel (including angioplasty and surgery) being required was slightly increased between 6 and 12 months of follow-up. Similarly, the rate of AMI, as well as the mortality rate, remained unchanged.

Therefore, we conclude that the LASER is safe and effective in the treatment of in-stent restenosis. The values of the clinical variables favor the LASER during the first 6 months of follow-up as compared with the results found in the literature about patients treated only with the balloon. There was a slight increase in the number of new procedures performed in the vessel treated with LASER + balloon between 6 and 12 months of follow-up. Finally, a randomized study comparing LASER versus balloon would be required to assess if the LASER has more advantages than the balloon in treating in stent new restenosis. Although feasible, conducting a randomized study seems unlikely in the near future, considering the fact that studies with intracoronary radiation are beginning to be conducted.

Limitations of the study – In spite of the small sample size, each case was carefully assessed under a strict protocol. Although this was not a randomized study, as already mentioned, we assessed the first 33 reports of patients with in-stent restenosis, treated with LASER. At the Miami Heart Institute, most patients with in-stent restenosis are treated with LASER.

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Basic Science Review

Pimecrolimus and Dual Pimecrolimus-Paclitaxel Eluting Stents Decrease Neointimal Proliferation in a Porcine Model

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Objectives and Background: The purpose of this study was to determine the effectiveness and vascular response of a pimecrolimus drug eluting stent and a combination (pimecrolimus + paclitaxel) stent as compared with bare metal controls in the porcine coronary model. **Methods and Results:** In the first phase of the study, cobalt chromium stents were loaded with an erodible polymer and either a slow release or a fast release formulation of pimecrolimus. Thirty stents (metal, $n = 10$; pimecrolimus slow, $n = 10$; pimecrolimus fast, $n = 10$) were implanted in the coronary arteries of 10 pigs. At 30 days, neointimal proliferation and inflammation were both significantly less in the pimecrolimus fast release group as compared with the bare metal controls. Endothelialization was complete and equal in all three groups of stents. In the second phase of the study, stents were loaded with an erodible polymer with alternating reservoirs of paclitaxel and pimecrolimus. Twenty stents (8 control stents and 12 dual stents) were implanted in the coronary arteries of seven pigs. At 30 days, neointimal proliferation was significantly less in the dual drug group as compared with the bare metal controls. Endothelialization was complete in both groups of stents, suggesting complete healing of the arteries. **Conclusions:** In a 30-day porcine stent model, pimecrolimus inhibits neointimal proliferation as compared with bare metal stents. Also, the proof of concept of a dual drug eluting stent was established showing both safety and efficacy.

Key words: restenosis; animal models of human disease; vascular biology

INTRODUCTION

Drug eluting stents (DES) have significantly decreased restenosis rates after percutaneous coronary intervention [1,2]. However, in patients with diabetes and other high risk attributes, clinical and angiographic restenosis rates above 10% may be seen [3,4]. A further potential limitation of current DES designs is the phenomenon of delayed stent thrombosis, the exact frequency of which is unknown. Therefore, the opportunity exists for the development of DES devices with improved safety and efficacy.

To date, human efficacy has been demonstrated with only two classes of pharmaceutical agents. Rapamycin (sirolimus) and its derivatives have both anti-inflammatory and direct anti-proliferative properties [5]. The anti-inflammatory effects are mediated via inhibition of iNos and cox2 gene expression [6] and the anti-proliferative effects derive from inhibition of the mTOR oncogene. The relative importance of these two actions is incompletely understood. Paclitaxel inhibits mitosis

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